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Excretion and Tissue Disposition of Dichloroacetonitrile in Rats and Mice

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The excretion and tissue distribution of [1-^{14}C]dichloroacetonitrile and [2-^{14}C]dichloroacetonitrile were studied in male Fischer 344 rats and male B6C3F1 mice. Three dose levels of dichloroacetonitrile (DCAN) (0.2, 2, or 15 mg/kg) were administered to rats and two dose levels of DCAN (2 or 15 mg/kg) to mice. Daily excreta including exhaled volatiles and radiolabeled carbon dioxide ($^{14}CO_2$) were analyzed for radiolabeled carbon (^{14}C) until > 70% of the radioactivity was excreted. At that time the animals were sacrificed and tissues were collected. Tissues and excreta were analyzed for ^{14}C by combustion and liquid scintillation counting. Rats administered [1-^{14}C]DCAN excreted 62 to 73% of the ^{14}C in 6 days, with 42 to 45% in urine, 14 to 20% in feces, and 3 to 8% as CO_2. Rats administered [2-^{14}C]DCAN excreted 82 to 86% of the ^{14}C in 48 hr, with 35 to 40% in urine, 33 to 34% as CO_2, and 10 to 13% in feces. Mice administered [1-^{14}C]DCAN excreted 83 to 85% of the ^{14}C in 24 hr, with 64 to 70% in urine, 9 to 13% in feces, and 5 to 6% as CO_2. Mice administered [2-^{14}C]DCAN excreted 84 to 88% of the ^{14}C in 24 hr with 42 to 43% in urine, 8 to 11% in feces, and 31 to 37% as CO_2. Liver tissues retained the most ^{14}C in all studies except the study of [1-^{14}C]DCAN in rats, where blood contained the most ^{14}C.

These results indicate that DCAN was absorbed rapidly after oral administration in water. The differences in the route of excretion of [1-^{14}C]DCAN compared to [2-^{14}C]DCAN indicated that the molecule was being cleaved in the body and metabolized by different mechanisms.

Introduction

The chlorination of drinking water results in the formation of by-products including trihalomethanes and halogenated acetonitriles. Dihaloacetonitriles have been found in chlorinated drinking water at a concentration of 0.3 to 8.1 ppb (*1*). Haloacetonitriles bind to polyadenylic acid without enzymatic activation. They also induce DNA strand breakage in cultured human CCRF-CEM cells (*2*). Several haloacetonitriles induced tumors when applied to the skin of SENCAR mice (*3*). Therefore, haloacetonitriles possess the potential for carcinogenic activity.

This paper examines the excretion and organ distribution of dichloroacetonitrile (DCAN) after oral administration to rats and mice as a part of the toxicity studies for this compound. We have examined these parameters with DCAN radiolabeled on each of the two carbon atoms. Differences in disposition of these two radiolabeled compounds determine if the molecule is degraded into one-carbon fragments.

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Methods

The [1-^{14}C]DCAN (specific activity 5.0 mCi/mmole) and [2-^{14}C]DCAN (specific activity 4.04 mCi/mmole) were purchased from New England Nuclear (Boston, MA). These radiolabeled compounds were purified by distillation in a molecular still (Ace Glass Co., Vineland, NJ) before the dosing solutions were prepared. Purity of the compounds was > 98% as measured by reverse-phase, high-performance liquid chromatography (HPLC) when the dosing solutions were prepared, but slow degradation of the compound occurred after preparation. HPLC conditions included a solvent of 1:1 (v/v)acetonitrile:water on a 10 μ C_{18} Alltech (Deerfield, IL) column using ultraviolet detection at 195 nm. Unlabeled DCAN purchased from Pfaltz and Bauer (Waterbury, CT) was determined to be > 98% pure by gas liquid chromatography (GLC) using a 30 m OV 1701 capillary column and a flame ionization detector.

Male Fischer 344 rats weighing 170–250 g and male B6C3F1 mice weighing 18–25 g at the time of administration were purchased from Harlan Sprague-Dawley (Walkersville, MD). Animals were housed individually in glass metabolism cages (Vanguard International, Neptune, NJ) designed to collect all excreta separately. Exhaled carbon dioxide (CO_2) was collected in a 100 mL volume of solution of 2:1 (v/v)Carbosorb (Packard In-

struments, Downers Grove, IL): ethylene glycol, and unchanged DCAN collected in 25 mL of 2-methoxyethyl ether (*Aldrich Chemicals, Milwaukee, WI*). Food (Wayne Lab Blox, Chicago, IL) and water were provided *ad libitum*, and the animals were maintained on a 12-hr light-dark cycle.

Three dose levels (15.0, 2.0, or 0.20 mg/kg) were orally administered to rats (n = 3), and two dose levels (15.0 or 2.0 mg/kg) were orally administered to mice (n = 3). Dosing solutions for rats were prepared in water such that each animal received 40 μCi/kg for the 15 and 2 mg/kg doses in a 0.3 to 0.5 mL volume. The 0.2 mg/kg dose in rats was limited to 9 μCi/kg because of the specific activity of the radiolabel. Dosing solutions for mice were prepared in water such that each animal received 10 μCi at the 15 mg/kg dose. The 2 mg/kg dose was limited to 2 μCi per animal, and the 0.2 mg/kg dose could not be prepared because of specific activity limitations. Urine, feces, and expired air were collected daily and counted for radioactivity; the percentage of dose excreted per day was calculated except for those mice from which a 6.5-hr sample was also taken. The experiments were continued until > 70% of the radiolabeled carbon (^{14}C) was excreted, at which point the animals were sacrificed. This condition was met at 6 days for [1-^{14}C]DCAN, at 2 days for [2-^{14}C]DCAN in rats, and at 24 hr in mice. Urine samples (combined with the cage wash) (0.5–1 mL), Carbosorb/ethylene glycol, and 2-methoxyethyl ether solutions were counted after addition to Beta Phase scintillation fluid (Westchem Products, San Diego, CA). A Beckman LS2800 (Beckman Instruments, Fullerton, CA) was used for liquid scintillation counting (LSC). Feces (combined with intestinal contents) were homogenized in 5 mL/g of 1N KOH in water. Samples of the homogenates were combusted to $^{14}CO_2$ in a Packard Tri Carb (Packard Instrument Co., Downers Grove, IL) sample oxidizer and quantified for radioactivity by LSC. Animals were sacrificed by CO_2 inhalation, and blood samples were obtained by cardiac puncture. At sacrifice, brain, lung, liver, kidney, small and large intestine, stomach, testes, and samples of adipose tissue (testicular), skin, and muscle were removed. Organs were weighed, and 0.1 g samples were combusted in the tissue oxidizer as described above. For nondiscrete tissues in rats (blood, adipose tissue, skin, and muscle) total tissue weights were estimated as 9, 7, 16 and 50% of body weight respectively (*4*). For mice, the corresponding tissue weight estimates were 7.6, 9.8, 14.5, and 45%, respectively (*5*). The percentage of dose was calculated for all tissues at each time point.

Statistical comparisons were determined by analysis of variance and least significant difference tests. Differences were considered significant at $p < 0.05$.

Results

To determine if the dose affected the excretion or disposition of DCAN, the animals were orally administered 0.2, 2.0, and 15 mg/kg [^{14}C]DCAN. The highest dosage level represented 5–10% of the oral LD_{50} value of 2 mmole/kg determined for rats (data not presented). DCAN radiolabeled on each carbon atom was administered to measure differences in the excretion or disposition of the individual carbon atoms.

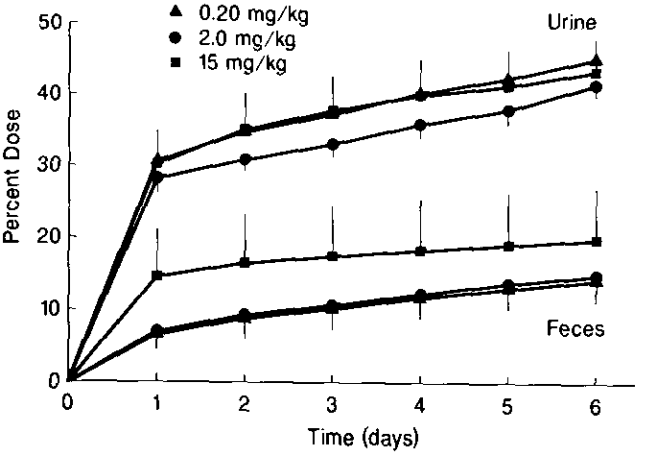


FIGURE 1. Cumulative excretion of [1-^{14}C] DCAN (as ^{14}C equivalents) after oral administration to rats: (□)15 mg/kg; (○)2 mg/kg; (△)0.20 mg/kg as aqueous solutions. Values are expressed as percentage of administered dose, $\bar{x}$ ± SD, n = 3.

[1-^{14}C]DCAN in Rats

Between 40 and 54% of the [1-^{14}C]DCAN dose was excreted within 24 hr at all dose levels (Fig. 1). After 48 hr, the rate of excretion decreased slowly to a range of 2 to 4% per day. By 6 days, 62 to 73% of the dose had been eliminated. At this time, most of the excreted radioactivity was recovered in the urine (42 to 45% of the dose). Lesser amounts were found in feces (14 to 20%) and in exhaled air. The exhaled air contained 3 to 8% of the dose as carbon dioxide with less than 1% appearing in the organic trap (Table 1). Analysis of variance comparing the percentage of administered ^{14}C excreted versus the dose level showed that the fecal elimination and carbon dioxide exhalation were significantly greater at the 15 mg/kg dose than at the lower doses. The carbon dioxide exhalation at 2 mg/kg was also greater than the 0.2 mg/kg dose, and the urinary excretion was lower at the 2 mg/kg dose than the other doses.

After 6 days, the tissues retained 19.3% of the dose.

Table 1. Cumulative expiration of [1-^{14}C]DCAN (as ^{14}C equivalents) 48 hr after oral administration to rats.[a]

	[1-^{14}C]DCAN, % of dose		
	15 mg/kg	2.0 mg/kg	0.20 mg/kg
CO_2	8.1 ± 2.5	5.2 ± 0.6	3.2 ± 0.2
Organic	0.8 ± 0.2	0.4 ± 0.1	N.S.[b]

[a]Values are expressed as percentage of administered dose. $\bar{x}$ ± SD, n = 3.
[b]N.S. = not sampled.

Table 2. Tissue levels of (1-^{14}C)DCAN (as ^{14}C equivalents) 6 days after oral administration to rats.[a]

Tissue	Tissue levels of [1-^{14}C]DCAN, % of dose		
	15 mg/kg	2.0 mg/kg	0.20 mg/kg
Blood	7.22 ± 1.44	7.89 ± 1.01	4.12 ± 1.36
Liver	1.88 ± 0.34	2.60 ± 0.35	2.13 ± 0.33
Muscle	3.88 ± 0.47	6.88 ± 0.76	7.88 ± 1.68
Skin	3.32 ± 0.37	6.25 ± 0.92	6.13 ± 0.24
Kidney	0.35 ± 0.05	0.44 ± 0.04	0.37 ± 0.01
Adipose tissue	0.48 ± 0.08	0.57 ± 0.06	0.63 ± 0.08
Gastrointestinal	0.97 ± 0.24	1.60 ± 0.17	1.91 ± 0.28
Brain	0.06 ± 0.01	0.06 ± 0.01	0.05 ± 0.01
Lung	0.14 ± 0.02	0.20 ± 0.06	0.17 ± 0.04
Testes	0.14 ± 0.03	0.27 ± 0.05	0.23 ± 0.06
Total recovery	90.44 ± 1.52	90.42 ± 1.01	89.13 ± 2.13

[a]Values are expressed as percentage of administered dose, $\bar{x}$ + SD, n = 3. Recovery include radioactivity from tissues and all excreta.

Table 3. Tissue levels of (2-^{14}C) DCAN (as ^{14}C equivalents) 2 days after oral administration to rats.[a]

Tissue	Tissue levels of [2-^{14}C]DCAN, % of dose		
	15 mg/kg	2.0 mg/kg	0.20 mg/kg
Blood	4.57 ± 1.99	2.02 ± 0.60	2.47 ± 0.19
Liver	5.67 ± 0.54	5.23 ± 0.32	5.70 ± 0.45
Muscle	3.37 ± 1.07	2.74 ± 0.96	4.78 ± 0.51
Skin	1.62 ± 0.24	0.94 ± 0.02	1.61 ± 0.06
Kidney	0.47 ± 0.04	0.37 ± 0.01	0.47 ± 0.03
Adipose tissue	0.31 ± 0.02	0.35 ± 0.12	0.93 ± 0.27
Gastrointestinal	0.71 ± 0.13	0.59 ± 0.04	0.76 ± 0.09
Brain	0.08 ± 0.02	0.05 ± 0.01	0.08 ± 0.00
Lung	0.12 ± 0.01	0.07 ± 0.01	0.10 ± 0.02
Testes	0.10 ± 0.01	0.07 ± 0.01	0.12 ± 0.01
Total recovery	100.54 ± 6.16	94.44 ± 5.89	103.47 ± 6.08

[a]Values are expressed as percentage of administered dose, $\bar{x}$ ± SD, n = 3. Recovery includes radioactivity from tissues and all excreta.

Blood retained the highest amount (4 to 8%) followed by muscle (4 to 8%), skin (3 to 6%), and liver (2 to 3%) (Table 2). Total recovery of administered ^{14}C in tissues, body fluids, urine, and feces found in this study ranged from 89.1 to 90.4%.

[2-^{14}C]DCAN in Rats

At the three dose levels of [2-^{14}C]DCAN, between 71 and 78% of the dose was excreted within 24 hr (Fig. 2). This percentage had increased to 82 to 86% of the dose at 48 hr when the experiment was terminated. The urine contained 35 to 40% of the ^{14}C after 48 hr. The expired air contained 33 to 34% of the dose with 0.28 to 0.37% of the dose in the organic trap (data not shown) and the remainder as carbon dioxide. Lesser amounts were found in feces (10 to 13%). Analysis of variance comparing the percentage of administered ^{14}C excreted versus the dose level showed no significant differences in excretion among these doses.

After 2 days, the tissues retained 12 to 17% of the dose. Liver retained the highest amount (5.2 to 5.7%) followed by muscle (3 to 5%), blood (2 to 5%) and skin (1 to 2%) (Table 3). Total recovery of administered ^{14}C in tissue, body fluids, urine, and feces found in this study ranged from 94 to 103%.

[1-^{14}C]DCAN in Mice

The excretion of [1-^{14}C]DCAN was substantially more rapid in B6C3F1 mice than in F-344 rats. At the 15 and 2.0 mg/kg dose levels tested, 84.6 and 82.5%, respectively, of the dose were eliminated by 24 hr. The urine contained 69.7% of the 15 mg/kg dose and 63.5% of the 2 mg/kg dose, and the feces contained 9.1 and 13.1%, respectively (Fig. 3). Only 0.43% of the 15 mg/kg dose and 0.31% of the 2 mg/kg dose were expired as organics, whereas at these doses, 5.3 to 5.6% was expired as CO_2. Statistical tests comparing the percentage of administered ^{14}C excreted versus the dose level showed an increased fecal elimination at the lower dose.

After 24 hr, the tissues contained 11 to 12% of the dose. The liver had the highest amount of radioactivity (3.5 to 4.2% of the dose) followed by almost equal amounts in muscle and skin (1.6 to 2.1%) and in blood

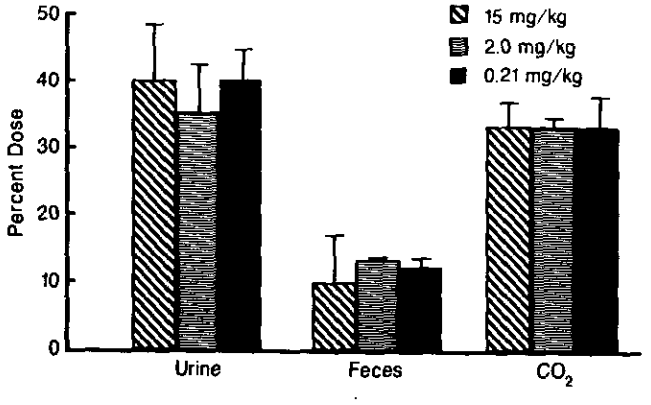


Figure 2. Cumulative excretion of (2-^{14}C) DCAN (as ^{14}C equivalents) after oral dosing to rats. Administered in 15, 2, and 0.21 mg/kg aqueous solutions. Values are expressed as percentage of administered dose, $\bar{x}$ ± SD, n = 3.

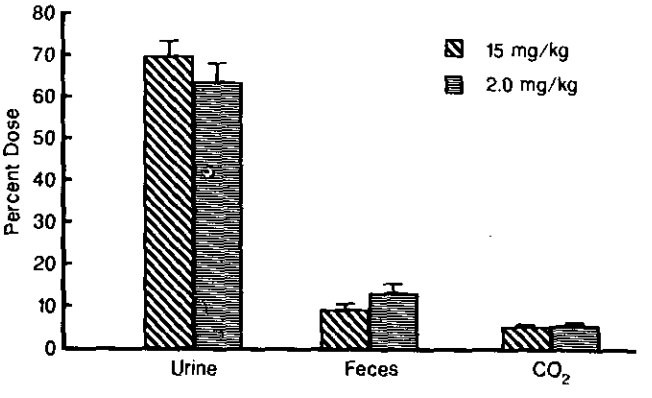


FIGURE 3. Cumulative excretion of (1-^{14}C) DCAN (as ^{14}C equivalents) after oral administration to mice. Administered in 15 and 2 mg/kg aqueous solutions. Values are expressed as percentage of administered dose, $\bar{x}$ ± SD, n = 3.

Table 4. Tissue levels of (1-^{14}C) DCAN (as ^{14}C equivalents) 1 day after oral administration to mice.[a]

Tissue	Tissue levels of [1-^{14}C]DCAN, % of dose	
	15 mg/kg	2.0 mg/kg
Blood	1.11 ± 0.28	0.95 ± 0.19
Liver	3.48 ± 0.43	4.25 ± 0.35
Muscle	2.11 ± 0.53	1.56 ± 0.11
Skin	2.02 ± 0.55	1.69 ± 0.21
Kidney	0.38 ± 0.10	0.46 ± 0.02
Fat	1.22 ± 0.55	0.89 ± 0.23
Gastrointestinal	1.46 ± 0.27	1.59 ± 0.27
Brain	0.04 ± 0.02	0.03 ± 0.01
Lungs	0.08 ± 0.04	0.07 ± 0.01
Testes	0.05 ± 0.03	0.04 ± 0.02
Total recovery	97.55 ± 1.12	95.49 ± 3.12

[a]Values are expressed as percentage of administered dose, $\bar{x}$ ± SD, n = 3. Recovery include radioactivity from tissues and all excreta.

Table 5. Tissue levels of (2-^{14}C) DCAN (as ^{14}C equivalents) 1 day after oral administration to mice.[a]

Tissue	Tissue levels of [2-^{14}C] DCAN, % of dose	
	15 mg/kg	2.0 mg/kg
Blood	0.29 ± 0.07	0.27 ± 0.08
Liver	5.12 ± 1.14	5.37 ± 0.43
Muscle	1.03 ± 0.06	0.79 ± 0.21
Skin	0.45 ± 0.04	0.52 ± 0.09
Kidney	0.56 ± 0.15	0.50 ± 0.04
Fat	0.62 ± 0.05	0.38 ± 0.11
Gastrointestinal	0.65 ± 0.12	0.80 ± 0.26
Brain	0.04 ± 0.01	0.03 ± 0.01
Lungs	0.04 ± 0.01	0.03 ± 0.01
Testes	0.02 ± 0.00	0.05 ± 0.05
Total recovery	92.94 ± 3.55	96.55 ± 2.15

[a]Values are expressed as percentage of administered dose, $\bar{x}$ ± SD, n = 3. Recovery includes radioactivity from tissues and all excreta.

and fat (0.9 to 1.2%) (Table 4). Total recovery was 97.6 and 95.2% for the 15 and 2 mg/kg doses, respectively.

[2-^{14}C]DCAN in Mice

The [2-^{14}C]DCAN was also excreted rapidly with 83.8% of the 15 mg/kg dose and 88.0% of the 2 mg/kg dose eliminated in 24 hr. The urine contained the largest amount of radioactivity, with 42 to 43% of the dose at the two doses tested (Fig. 4). The CO_2 found in expired air contained 31 to 37% of the administered radioactivity. Lesser amounts were found in feces: 11% of the dose was recovered at the 15 mg/kg dose and 7.5% at the 2 mg/kg dose. Small amounts of radioactivity (0.2 to 0.4%) were found in the organic trap in expired air. Statistical tests comparing the percentage of administered ^{14}C eliminated versus the dose level showed greater fecal elimination at the high dose and greater carbon dioxide exhalation at the lower dose.

After 24 hr, the tissues contained about 9% of the dose. The liver contained most of the radioactivity (~5% of the dose) with smaller amounts found in muscle (0.8 to 1.0%), kidney (0.5 to 0.6%), and skin (0.45 to 0.52%) (Table 5). All other tissues contained less than 0.5% of the dose. Total recovery was 92.9% for the 15 mg/kg dose and 96.6% for the 2 mg/kg dose.

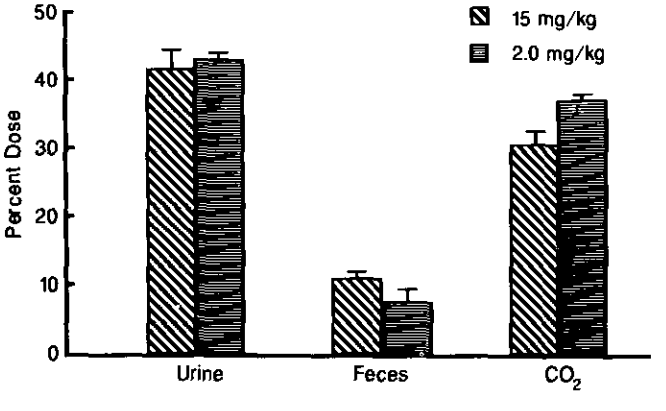


FIGURE 4. Cumulative excretion of (2-^{14}C) DCAN (as ^{14}C equivalents) after oral dosing to mice. Administered in 15 and 2 mg/kg aqueous solutions. Values are expressed as percentage of administered dose, $\bar{x}$ ± SD, n = 3.

Discussion

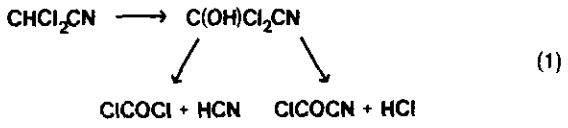
The use of DCAN radiolabeled at the two different carbon atoms allowed us to determine if the molecule was degraded into one-carbon fragments. Substantial differences in the rate and route of excretion of [1-^{14}C]DCAN, labeled on the cyanide (CN) group compared to [2-^{14}C]DCAN, labeled on the dichloromethyl group, were found in rats. In mice, the major differences between these labeled compounds were in the route of excretion.

After oral administration, DCAN was rapidly absorbed in rats and mice. If all the radioactivity that appeared in the feces was unabsorbed material, then absorption would be estimated at approximately 90% of the dose. Since bilary excretion may account for some DCAN or its metabolites found in feces, absorption may be greater than 90%. Statistically significant differences in fecal elimination were found when the different doses of [1-^{14}C]DCAN were compared, but they were not observed for [2-^{14}C]DCAN. These fecal elimination differences cannot reflect absorption limitations, as both labeled compounds would act in a similar manner and must reflect differences in metabolism or elimination.

Significant differences in the amount of $^{14}CO_2$ formation were found for [1-^{14}C]DCAN and [2-^{14}C]DCAN in rats and mice. For [1-^{14}C]DCAN, about 5% of the radioactivity was eliminated as $^{14}CO_2$, whereas for [2-^{14}C]DCAN, about 35% was eliminated in both rats and mice. The $^{14}CO_2$ exhalation was essentially complete in 24 hr even though urinary and fecal excretion rates were quite different between rats and mice.

These results are consistent with the postulated metabolism of DCAN. Pereira and workers (*6*) proposed that DCAN would be metabolized to cyanide and phosgene or formyl chloride. The active intermediate could

also degrade to form chloride ion and formyl cyanide[Eq. (1)]. The two pathways will lead to the same degradation products—chlorine, formic acid, CO_2, and CN. These experiments cannot distinguish the different pathways but can determine the fate of each carbon atom. If the metabolism of DCAN was rapid, [1-^{14}C]DCAN would be expected to be excreted like cyanide ion and [2-^{14}C]DCAN like a molecule producing phosgene or formyl chloride.



(1)

The disposition and excretion of [1-^{14}C]DCAN was similar to results from studies on the disposition of cyanide. Cyanide administered intravenously to rats formed about 8% $^{14}CO_2$ in 7 days (*7*). The major route of excretion after cyanide administration was the urine; in 24 hr, 45% of the radiolabeled dose was excreted in the urine and this percentage increased to 68% at 7 days. Our studies showed a 24-hr urinary excretion of 28 to 31% in rats and 38 to 44% of the radiolabeled dose in mice. A total of 42 to 45% of the dose appeared in the urine by 6 days in rats. The feces contained 14% of the dose by 7 days in the cyanide studies compared to 14 to 20% in 6 days in our studies. Major tissues containing radioactivity after cyanide dosing were blood (values not given), gastrointestinal tract (4.1%), muscle (1.8%), and liver (0.6%). Blood, muscle, and liver had the highest radioactivity levels after administration of [1-^{14}C]DCAN. The gastrointestinal tract levels were only 1 to 2% for DCAN and were less than those found for cyanide. Cyanide appeared to concentrate in the gastrointestinal tract after being trapped in the stomach. After administration of [^{14}C]cyanide, radioactivity was found in several endogenous compounds including choline, methionine, allantoin, and fatty acids (*8*). The cyanide carbon probably entered the one-carbon pool through formation of the formate ion, and a slow elimination of radioactivity occurred after the first few days. These findings are consistent with the slow elimination of [1-^{14}C]DCAN in rats. Another indication that cyanide was formed from DCAN was the increased urinary thiocyanite levels found by Pereira and coworkers (*6*) after administering DCAN to rats.

The metabolism of [2-^{14}C]DCAN would result in the formation of radiolabeled phosgene in a manner analogous to chloroform. Chloroform is metabolized to phosgene, and this reactive intermediate reacts with proteins and amino acids or is further degraded to CO_2 (*9*, *10*). The recoveries in excreta of chloroform and [2-^{14}C]DCAN are difficult to compare since the predominant route of chloroform elimination is exhalation of unchanged compound. The total amount of $^{14}CO_2$ collected after oral [^{14}C]chloroform administration of 60 mg/kg to rats was 66%, and the amount of ^{14}C excreted in the urine and feces was 7.6% (*11*). Approximately equal amounts of radioactivity were found in CO_2 and in urine after oral administration of [2-^{14}C]DCAN in rats and mice. These differences between chloroform and DCAN may be caused by the presence of other metabolic routes for DCAN. Protein binding of ^{14}C to liver was found both after [^{14}C]chloroform administration (*9*) and after [^{14}C]DCAN administration (*2*).

The differences in excretion rates between rats and mice may result from a higher rate of metabolism in the mouse for compounds such as chloroform (*11*) or from different routes of metabolism. Urinary metabolites must be identified before these possibilities can be distinguished.

Some dose-related differences in excretion were noted in these studies. These differences were particularly notable for the CO_2 exhalation in rats administered [1-^{14}C]DCAN and for fecal elimination and carbon dioxide exhalation in mice administered [2-^{14}C]DCAN. Since these differences were not seen for DCAN labeled on the other carbon atom in the same species, the effects probably did not result from the absorption or metabolism of DCAN. Rather, they resulted from metabolism or excretion of the metabolic products and will require metabolite identification for interpretation.

In summary, DCAN was rapidly absorbed in rats and mice after oral administration. Differences in the route of excretion of [1-^{14}C]- and [2-^{14}C]DCAN indicated that the molecule was cleaved in the body and that the major differences were in the extent of CO_2 formation. Mice excreted both labeled compounds by the same routes as rats, but the rate of excretion was much more rapid. Distribution after > 70% of the radioactivity had been excreted showed that the liver contained the highest amount of the dose except in the study of [1-^{14}C]DCAN in rats in which the highest levels of the dose were found in the blood.

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